

WHAT IS CLAIMED IS:

1. A method of treating or reducing the risk of acquiring a condition selected from the group consisting of osteoporosis, hypercholesterolemia, hyperlipidemia, atherosclerosis, breast cancer, endometrial cancer, uterine cancer, ovarian cancer, vaginal dryness and loss of muscle mass, said method comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3 β ,17 β -diol and 4-androstene-3,17-dione in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

2. A pharmaceutical composition comprising:

- a) a pharmaceutically acceptable excipient, diluent or carrier;
- b) a therapeutically effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3 β ,17 β -diol, 4-androstene-3,17-dione and a prodrug that is converted *in vivo* into any of the foregoing sex steroid precursors; and
- c) a therapeutically effective amount of at least one selective estrogen receptor modulator .

3. A kit comprising a first container containing a therapeutically effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3 β ,17 β -diol, 4-androstene-3,17-dione and any prodrug that is converted *in vivo* any into the foregoing precursors; and further comprising a second container containing a therapeutically effective amount of at least one selective estrogen receptor modulator .

4. The method of claim 1 further comprising the step of administering a therapeutically effective amount of a bisphosphonate as part of said combination therapy.

5. A kit of claim 3 comprising at least one additional container of said kit that contains a therapeutically effective amount of at least one bisphosphonate.

6. A pharmaceutical composition of claim 2 wherein said composition further comprising a therapeutically effective amount of at least one bisphosphonate.

7. The method of claim 1 further comprising administering a therapeutically effective amount of a progestin.

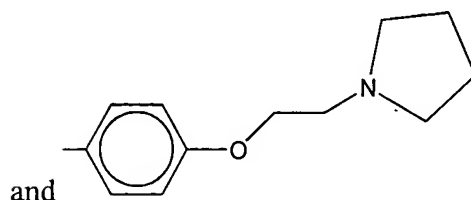
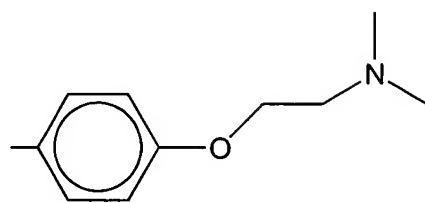
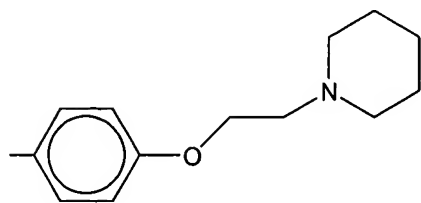
8. The method, pharmaceutical composition or kit of any of the foregoing claims wherein the precursor is not 4-androstene-3,17-dione.

9. A method of reducing the risk of acquiring breast cancer comprising administering to a patient for whom such reduction is desired, a prophylactically effective amount of a selective estrogen receptor modulator.

10. The method, pharmaceutical composition or kit of any of the foregoing claims 1 to 9 wherein the selective estrogen receptor modulator has a molecular formula with the following features :

- a) two aromatic rings spaced by 1 to 2 intervening carbon atoms, both aromatic rings being either unsubstituted or substituted by a hydroxyl group or a group converted *in vivo* to hydroxyl;
- b) a side chain possessing an aromatic ring and a tertiary amine function or salt thereof.

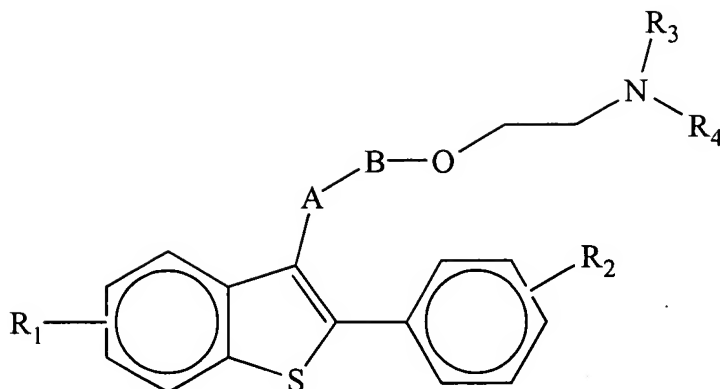
11. The method, pharmaceutical composition or kit of claim 10 wherein the side chain is selected from the group consisting of :



12. The method, pharmaceutical composition or kit of claim 10 wherein the two aromatic rings are both phenyl and wherein the side chain possesses a moiety selected from the group consisting of a methine, a methylene, -CO-, -O-, and -S-, an aromatic ring, and a tertiary amine function or salt thereof.

13. The method, pharmaceutical composition or kit of claim 10 wherein the selective estrogen receptor modulator is selected from the group consisting of a benzothiophene derivative, triphenylethylene derivative, indole derivative, benzopyran derivative, and centchroman derivative.

14. The method, pharmaceutical composition or kit of claim 10 wherein the selective estrogen receptor modulator is a benzothiophene derivative compound of the following formula:



wherein R₁ and R₂ are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl ;

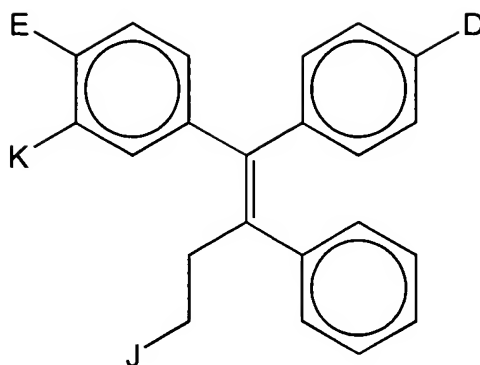
wherein R₃ and R₄ are either independently selected from the group consisting of : C1-C4 alkyl, or wherein R₃, R₄ and the nitrogen to which they are bound, together are any structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino;

wherein A is selected from the group consisting of -CO-, -CHOH, and -CH₂-;

wherein B is selected from the group consisting of phenylene, pyridylidene, and -cycloC₄H₂N₂-.

15. The method, pharmaceutical composition or kit of claim 14 wherein the selective estrogen receptor modulator is selected from the group consisting of Raloxifene, LY 353381 and LY 335563.

16. The method, pharmaceutical composition or kit of claim 10 wherein the selective estrogen receptor modulator is a triphenylethylene derivative compound of the following formula :

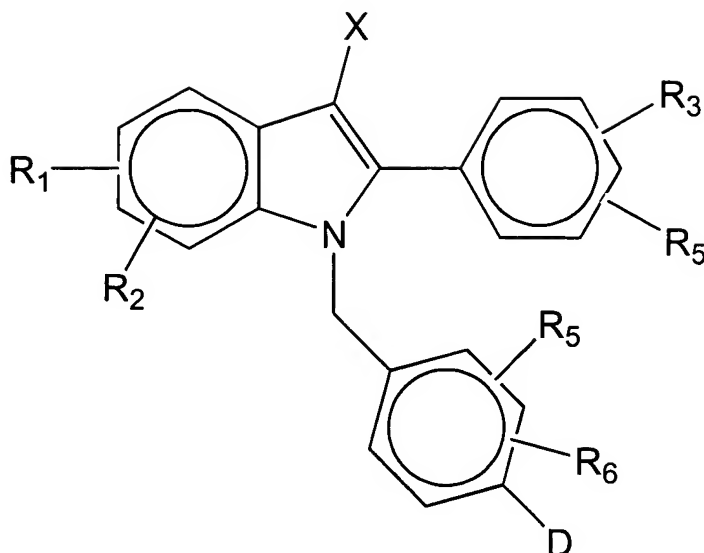


wherein D is $-\text{OCH}_2\text{CH}_2\text{N}(\text{R}_3)\text{R}_4$ or $-\text{CH}=\text{CH}-\text{COOH}$ (R_3 and R_4 either being independently selected from the group consisting of C1-C4 alkyl, or R_3 , R_4 , and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino);

wherein E and K are independently hydrogen or hydroxyl ; wherein J is hydrogen or halogen.

17. The method pharmaceutical composition or kit of any of the foregoing claims 1 to 9 wherein selective estrogen receptor modulator is Tamoxifen, OH-tamoxifen, Droloxifene, Toremifene, Iodoxifene, and GW5638.

18. The method, pharmaceutical composition or kit of Claim 10 wherein the selective estrogen receptor modulator is an indole derivative compound of the following formula:

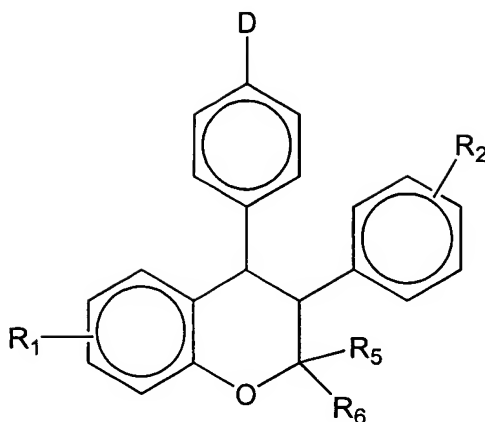


wherein D is selected from the groups consisting of $-OCH_2CH_2N(R_7)R_8$, $-CH=CH-CO N(R_7)R_8$, $-CC-(CH_2)_n-N(R_7)R_8$ (R_7 and R_8 either being independently selected from the group consisting of C_1-C_6 alkyl, or R_7 , R_8 and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring);

wherein X is selected from the group consisting of : hydrogen, and C_1-C_6 alkyl;

wherein R_1 , R_2 , R_3 , R_4 , R_5 , and R_6 are independently selected from the group consisting of : hydrogen, hydroxyl, C_1-C_6 alkyl, and a moiety converted in vivo in hydroxyl.

19. The method, pharmaceutical composition or kit of claim 10 wherein the selective estrogen receptor modulator is a centchroman derivative compound of the following formula :



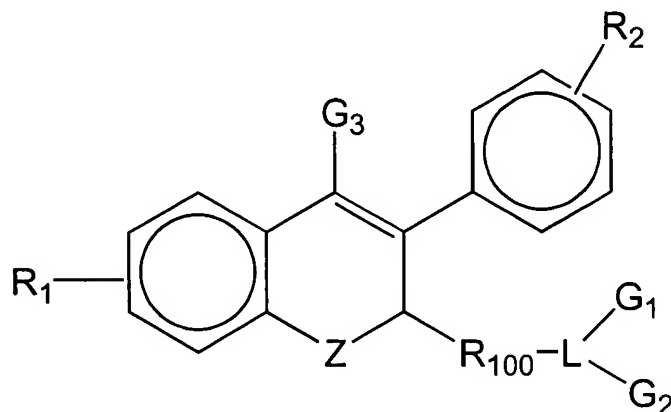
wherein R_1 and R_2 are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl;

wherein R_5 and R_6 are independently hydrogen or C_1 - C_6 alkyl ;

wherein D is $-OCH_2CH_2N(R_3)R_4$ (R_3 and R_4 either being independently selected from the group consisting of C_1 - C_4 alkyl, or R_3 , R_4 and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

20. The method, pharmaceutical composition or kit of claim 19 wherein the centchroman derivative is (3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

21. The method, pharmaceutical composition or kit of claim 10 wherein the selective estrogen receptor modulator has the following formula :



wherein R_1 and R_2 are independently hydrogen, hydroxyl or a moiety which is converted to hydroxyl in vivo ;

wherein Z is a bivalent closing moiety ;

wherein the R_{100} is a bivalent moiety which distances L from the B-ring by 4-10 intervening atoms ;

wherein L is a bivalent or trivalent polar moiety selected from the group of -SO-, -CON-, -N<, and -SON< ;

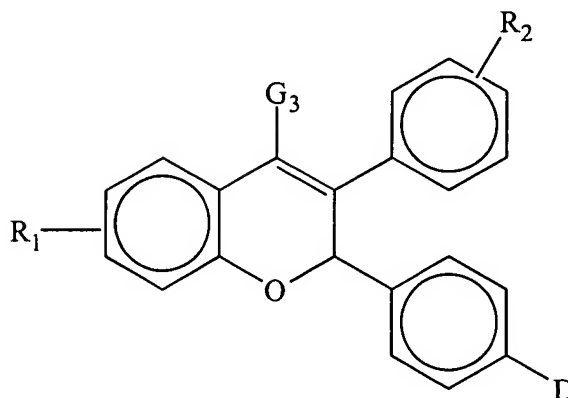
wherein G_1 is selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon or a bivalent moiety which joins G_2 and L to form a 5-to 7-membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing.

wherein G_2 is either absent or selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon or a bivalent moiety which joins G_1 and L to form a 5-to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing.

wherein G_3 is selected from the group consisting of hydrogen, methyl and ethyl.

22. The method, pharmaceutical composition or kit of claim 21, wherein Z is selected from the group consisting of -O-, -NH-, -S-, and -CH₂-.

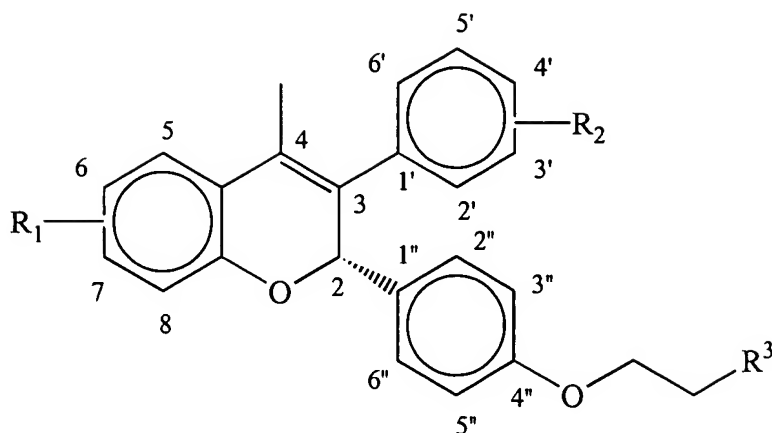
23. The method, pharmaceutical composition or kit of claim 22, wherein the compound is a benzopyran derivative of the following general structure :



wherein D is -OCH₂CH₂N(R₃)R₄ (R₃ and R₄ either being independently selected from the group consisting of C₁-C₄ alkyl, or R₃, R₄ and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

wherein R₁ and R₂ are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

24. The method, pharmaceutical composition or kit of claim 23, wherein the benzopyran derivative is an optically active compound having an absolute configuration S on carbon 2 or pharmaceutically acceptable salt thereof, said compound having the molecular structure:



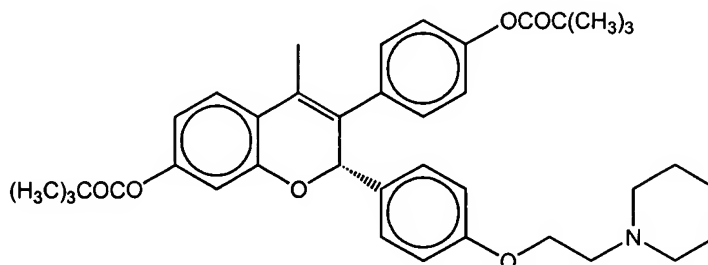
wherein R_1 and R_2 are independently selected from the group consisting of hydroxyl and a moiety convertible *in vivo* to hydroxyl;

wherein R^3 is a species selected from the group consisting of saturated, unsaturated or substituted pyrrolidinyl, saturated, unsaturated or substituted piperidino, saturated, unsaturated or substituted piperidinyl, saturated, unsaturated or substituted morpholino, nitrogen-containing cyclic moiety, nitrogen-containing polycyclic moiety, and $NRaRb$ (Ra and Rb being independently hydrogen, straight or branched C_1 - C_6 alkyl, straight or branched C_2 - C_6 alkenyl, and straight or branched C_2 - C_6 alkynyl).

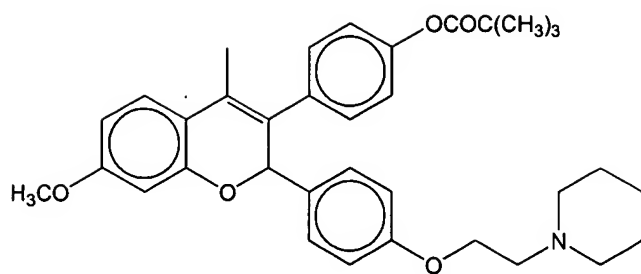
25. The method, pharmaceutical composition or kit of claim 24 wherein said compound or salt substantially lacks (2R)-enantiomer.

26. The method, pharmaceutical composition or kit of claim 23 where said selective estrogen receptor modulator is selected from the group consisting of:

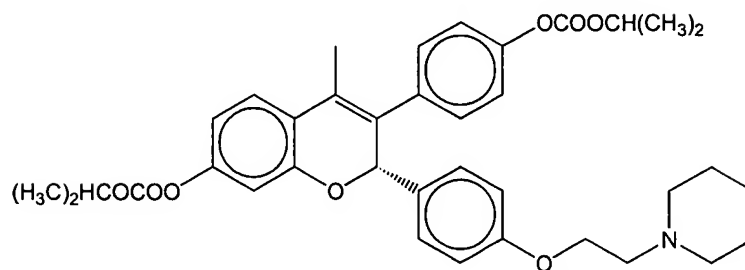
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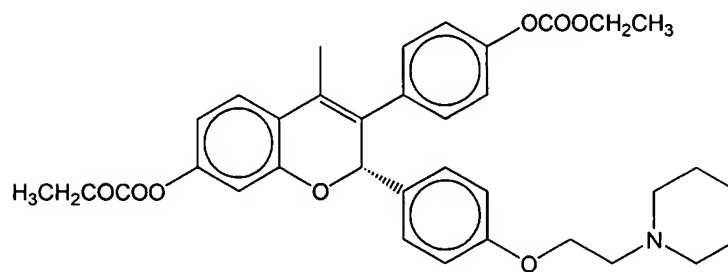
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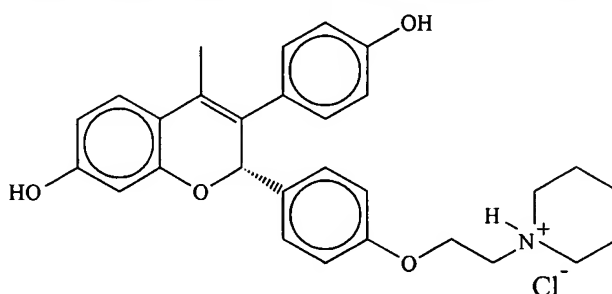


27. The method, pharmaceutical composition or kit of claim 23 wherein the benzopyran derivative is a salt of an acid selected from the group consisting of acetic acid, adipic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, fumaric acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, hydrochlorothiazide acid, hydroxy-naphthoic acid, lactic acid, maleic acid, methanesulfonic acid, methylsulfuric acid, 1,5-naphthalenedisulfonic acid, nitric acid, palmitic acid, pivalic acid, phosphoric acid, propionic acid, succinic acid, sulfuric acid, tartaric acid, terephthalic acid, p-toluenesulfonic acid, and valeric acid.

28. The method, pharmaceutical composition or kit of claim 27 wherein the acid is hydrochloric acid.

29. The method pharmaceutical composition or kit of any of the foregoing claims 1 to 9 wherein said selective estrogen receptor modulator is:

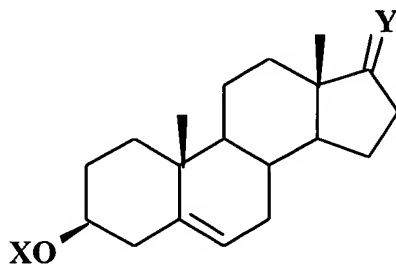
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and an amount of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3 β ,17 β -diol.

30. The method pharmaceutical composition or kit of any of the foregoing claims 1 to 9 wherein the sex steroid precursor is dehydroepiandrosterone.

31. The pharmaceutical composition or kit of claims 2, 3 or 8 wherein the compound converted *in vivo* to into sex steroid precursor has the general formula :

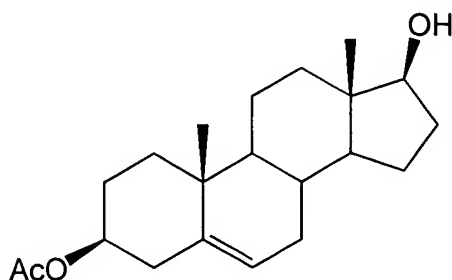


wherein X is selected from the group consisting of H- , ROC-, RCO₂CHRa- and RbSO₂- (R being selected from the group consisting of hydrogen, straight- or branched-(C₁-C₁₈) alkyl, straight- or branched-(C₂-C₁₈) alkenyl, straight- or branched-(C₂-C₁₈) alkynyl, aryl, furyl, straight- or branched-(C₁-C₁₈) alkoxy, straight- or branched-(C₂-C₁₈) alkenyloxy, straight- or branched-(C₂-C₁₈) alkynyloxy, aryloxy, furyloxy, and halogeno or carboxyl analogs of the foregoing; Ra being hydrogen or (C₁-C₆) alkyl; and, Rb being selected from the group consisting of hydroxyl (or salts thereof), methyl, phenyl and p-toluy);

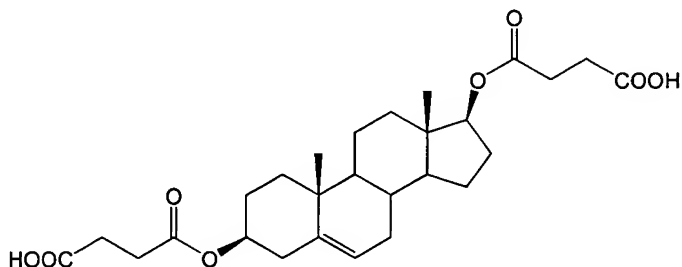
wherein Y is carbonyl oxygen or Y represent a β-OX (X having the same meaning as above) and α-H.

32. The pharmaceutical composition or kit of claims 2, 3 or 8 wherein the compound converted *in vivo* to into sex steroid precursor is selected from the group consisting of :

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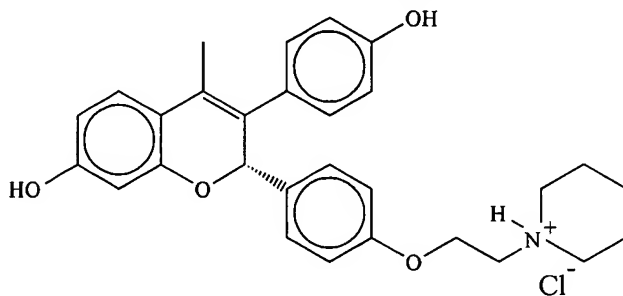


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33. A pharmaceutical composition comprising a pharmaceutically acceptable excipient diluent or carrier, a therapeutically effective amount of

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and a therapeutically effective amount of dehydroepiandrosterone.

34. A method of Claim 18 wherein the selective estrogen receptor modulator is TSE 424.